General

Guideline Title

Adjuvant interferon for malignant melanoma.

Bibliographic Source(s)

Alberta Provincial Cutaneous Tumour Team. Adjuvant interferon for malignant melanoma. Edmonton (Alberta): CancerControl Alberta; 2014 Feb. 13 p. (Clinical practice guideline; no. CU-002). [52 references]

Guideline Status

This is the current release of the guideline.

Regulatory Alert

FDA Warning/Regulatory Alert

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

- March 22, 2016 – Opioid pain medicines : The U.S. Food and Drug Administration (FDA) is warning about several safety issues with the entire class of opioid pain medicines. These safety risks are potentially harmful interactions with numerous other medications, problems with the adrenal glands, and decreased sex hormone levels. They are requiring changes to the labels of all opioid drugs to warn about these risks.

Recommendations

Major Recommendations

These recommendations were adapted from: Management of Malignant Melanoma: Best Practices, 2006 (Canadian Expert Panel on Malignant Melanoma) (see the "Adaptation" field).

- Enrollment in a clinical trial should be encouraged/considered.
- Most patients with in situ or early-stage melanoma will be cured by primary excision alone. Therefore, no standard adjuvant therapy is recommended for patients with melanoma that is in situ, less than 2 mm thick, 2–4 mm thick but non-ulcerated or node-negative.
- Patients with primary tumours that are 2.01–4.0 mm thick and ulcerated, deep primary tumours (T4), primary tumour of any thickness with

positive sentinel nodes or resected overt nodal disease, including patients who relapse in the nodal basin, should be referred to medical oncology for consideration for adjuvant therapy.

Features of High Risk (Smylie et al., 2006; Agarwala, 2002)
• Primary melanoma with tumour thickness ≥4.0 mm or Clark level V invasion • Primary melanoma with in-transit metastases • Primary melanoma with regional lymph node metastases that are clinically apparent or detected at elective lymph-node dissection • Regional lymph node recurrence • Involved nodes were excised but there was no known primary melanoma • Primary melanoma with tumour thickness 2.01–4.0 mm with ulceration

- Patients who are at high-risk for disease recurrence following complete surgical resection of the primary tumour are eligible for adjuvant treatment with interferon-alfa (IFNα).
- Prior to the initiation of treatment rule out metastatic disease:
  - Refer to staging guidelines (Balch et al., 2009) (see the Appendix in the original guideline document)
- Contraindications to interferon are:
  - A history of hypersensitivity to IFNα
  - Active cardiovascular disease (myocardial infarction within 6 months, active angina, or dysrhythmias)
  - Pre-existing liver disease
  - Central nervous system disease
  - Serious psychiatric conditions (including major depression)
  - Active autoimmune disease
  - Any debilitating medical condition is a relative contraindication because of the toxicities expected
- Before initiating high-dose adjuvant interferon therapy, the following baseline laboratory tests are required (Eggermont, 2002; Smylie et al., 2006):
  - Complete blood count (CBC)/differential
  - Hemoglobin
  - Hematocrit
  - Platelets
  - Blood chemistry including electrolytes
  - Liver function tests (LFTs; alanine aminotransferase/aspartate aminotransferase [ALT/AST])
  - Thyroid-stimulating hormone (TSH)
  - Additional testing, such as creatine phosphokinase (CPK) if abnormal troponin level, anti-thyroid antibodies and anti-nuclear antibodies, may be required

Treatment

- Pre-medication: acetaminophen 650 mg by mouth (PO) 30 minutes pre-intravenous (IV) IFNα and every 4–6 hours regularly during induction phase.
- Induction phase: 20 MU/m^2 intravenously 5 days per week for 4 weeks
  - Depending on the patient's performance status and symptoms, a rest period of 2 weeks between induction phase (weeks 1–4) and maintenance phase (weeks 5–52) may be considered ("BCCA protocol summary," 2006)
- Maintenance phase: 10 MU/m^2 subcutaneously 3 times per week for 48 weeks
- Laboratory tests should be performed weekly during induction phase and monthly during maintenance phase ("BCCA protocol summary," 2006):
  - CBC and differential, platelets, LFTs
  - Assessment for mood changes during clinic visits

Side Effects

- Fever, chills and rigors often occur when interferon therapy is first initiated but diminish over time.
- Treatment with IFNα is associated with a significant number of side effects that require close monitoring (Guillot et al., 2004; de Lemos, 2001; Kirkwood et al., 2002). These side effects may hamper reaching and maintaining the dose needed for maximal therapeutic effect (Sleijfer et al., 2005).
    - Common side effects are fatigue, fever, myalgia, anorexia, nausea, headache and chills ("flu-like" symptoms).
    - The incidence of severe neuropsychiatric disorders, such as depression, can be as high as 10% so close monitoring is recommended. Referral to a psychiatrist may be required.
    - The following are recommended to alleviate side effects:
        - Regular exercise to relieve fatigue.
        - Due to fluid losses through increased heart and metabolic rates, fever and sweats, an aggressive fluid hydration strategy is recommended. Administer 500 mL IV normal saline before each IV infusion. A daily oral intake of ≥2 litres of fluids, especially water, throughout therapy is advised. Avoid caffeine and alcohol containing beverages as they can cause dehydration.
        - Acetaminophen before each injection and/or at bedtime; consider another antipyretic/anti-inflammatory if acetaminophen is not effective.
        - Headaches are common. Tension-type headaches may require mild opioids. Migraine-like headaches may require treatment as for migraine.
        - Patients should be advised that side effects are worse on Mondays.
        - An anti-emetic (e.g., metoclopramide, prochlorperazine) may be required to relieve nausea; 5-hydroxytryptamine (5-HT3) antagonists can be helpful for chronic nausea.
        - Depression can be treated with antidepressants.
    - Long-term side effects that can result in dose alterations, disruptions and even discontinuation of therapy are (Agarwala, 2002):
        - Hepatotoxicity: Transient elevations in AST and ALT are common. Elevations more than five times the normal range require dose adjustment.
        - If radiation is to be part of the regimen, IFNα should not be given concurrently due to the risk of skin toxicity.
        - Patients with psoriasis may experience a worsening of their condition. This may require a dermatology consult.
        - Weight loss is common and patients may benefit from dietary counseling. If there is clinical concern, a dose reduction or cessation of therapy is indicated.
    - Potentially life-threatening side effects can occur but these are rare:
        - In the event of serious side effects, the dose should be held until the medical oncologist is contacted.
        - If the absolute neutrophil count (ANC) <500 cells/mL or ALT/AST >5–10 times normal, it is recommended that subsequent doses be held until the toxicity resolves re-initiation, which should be started at 50% of the previous IFNα dose.
        - Therapy should be discontinued if the ANC <250 cells/mL and/or ALT/AST >10 times normal.
        - Suicidal ideation has been reported and is a contraindication to further IFNα-2b therapy (Valentine et al., 1998).

Special Considerations

- The successful administration of IFNα-2b requires the services of a specialized and committed team of health care professionals, including physician, oncology nurse, social worker, pharmacist, and behavioral therapist or psychologist.
- Because hematologic and hepatic toxicity associated with high-dose interferon (HDI) therapy can be severe, ongoing monitoring is essential to ensure safety. White blood cell counts and liver function tests should be performed weekly during induction and monthly during maintenance therapy for at least 3 months, and then at least every 3 months in patients who are stable with no new complaints.
- Patient education is vital to help understand and anticipate the nature of the side effects and the interventions available to manage adverse events and preserve quality of life.
- During the maintenance phase, constitutional symptoms are managed by administering IFNα at bedtime with prophylactic antipyretics such as acetaminophen or ibuprofen.
- Meperidine may be useful for severe chills and rigors. Nausea and vomiting are uncommon but respond well to standard anti-emetics such as chlorpromazine or metoclopramide. Attention to fluid balance during IFNα therapy is critical. Because flu-like symptoms may cause dehydration, which tends to exacerbate other symptoms, proper hydration (≥2 L daily) must be ensured. Non-caffeinated fluids are preferred for oral and IV hydration (500–1000 mL daily) and may be used in selected patients. Antidepressants are effective in reducing fatigue and depression; prophylactic administration of these agents has been investigated (Musselman et al., 2001).

Follow-Up

- These patients will be seen by the attending medical oncologist monthly during the year of treatment, every 3 months for 2 more years and

then every 6 months thereafter in the outpatient clinic.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Malignant melanoma

Guideline Category

Management

Treatment

Clinical Specialty

Dermatology

Oncology

Radiation Oncology

Intended Users

Advanced Practice Nurses

Nurses

Physician Assistants

Physicians

Psychologists/Non-physician Behavioral Health Clinicians

Social Workers

Guideline Objective(s)

To provide information regarding adjuvant interferon-alfa (IFNα) being offered to patients who have been rendered disease-free following the resection of cutaneous melanomas and who are at high risk for subsequent recurrence

Target Population

Adults over the age of 18 years with malignant melanoma

Note: Different principles may apply to pediatric patients.

Interventions and Practices Considered

1. Encouraging enrollment in a clinical trial
2. Evaluation of patients at high risk for recurrence
3. Ruling out metastatic disease
4. Evaluation of contraindications to interferon
5. Baseline laboratory tests before initiating interferon therapy
6. Premedication with acetaminophen
7. Induction and maintenance phase dosing
8. Monitoring for and management of side effects, including ongoing monitoring of white blood cell counts and liver function tests (LFTs)
9. Use of specialized and committed team of health care professionals, including physician, oncology nurse, social worker, pharmacist, and behavioral therapist or psychologist
10. Patient education
11. Follow-up

Major Outcomes Considered

- Survival rates (5-year, disease-free, overall, recurrence-free, progression-free)
- Recurrence rates (5-year)
- Quality of life
- Adverse effects

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Research Questions

Specific research questions to be addressed by the guideline document were formulated by the guideline lead(s) and Knowledge Management (KM) Specialist using the PICO question format (patient or population, intervention, comparisons, outcomes).

Guideline Question

Should adjuvant interferon-alfa be offered to patients who have been rendered disease-free following the resection of cutaneous melanomas and who are at high risk for subsequent recurrence?

Search Strategy

The MEDLINE (1966 through December 2010), Cumulative Index to Nursing and Allied Health Literature (CINAHL), Cochrane, American Society of Clinical Oncology (ASCO) Abstracts and proceedings, and CANCERLIT databases were searched. The search included practice guidelines, systematic reviews, meta-analyses, randomized controlled trials, and clinical trials. Search terms included: interferon or adjuvant interferon and malignant melanoma.

PubMed was again searched in 2013 for evidence on adjuvant interferon in cutaneous melanoma. The search term "melanoma" was used and results were limited to clinical trials, published between January 2012 and January 2013. Citations were hand-searched for studies pertaining to interferon therapy.

Using the same search strategy, four relevant articles published between January 2013 and January 2014 were identified during the 2014 update.

Number of Source Documents

Four relevant articles published between January 2013 and January 2014 were identified during the 2014 update.

Methods Used to Assess the Quality and Strength of the Evidence

Not stated

Rating Scheme for the Strength of the Evidence

Not applicable

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Evidence was selected and reviewed by a working group comprised of members from the Alberta Provincial Cutaneous Tumour Team and a Knowledge Management (KM) Specialist from the Guideline Utilization Resource Unit (GURU). A detailed description of the methodology followed during the guideline development process can be found in the Guideline Utilization Resource Unit Handbook (see the "Availability of Companion Documents" field).

Evidence Tables

Evidence tables containing the first author, year of publication, patient group/stage of disease, methodology, and main outcomes of interest are assembled using the studies identified in the literature search. Existing guidelines on the topic are assessed by the KM Specialist using portions of the Appraisal of Guidelines Research and Evaluation (AGREE) II instrument (http://www.agreetrust.org) and those meeting the minimum requirements are included in the evidence document. Due to limited resources, GURU does not regularly employ the use of multiple reviewers to rank the level of evidence; rather, the methodology portion of the evidence table contains the pertinent information required for the reader to judge for himself the quality of the studies.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Formulating Recommendations

The working group members formulated the guideline recommendations based on the evidence synthesized by the Knowledge Management (KM) Specialist during the planning process, blended with expert clinical interpretation of the evidence. As detailed in the Guideline Utilization Resource Unit Handbook (see the "Availability of Companion Documents" field), the working group members may decide to adopt the recommendations of another institution without any revisions, adapt the recommendations of another institution or institutions to better reflect local practices, or develop their own set of recommendations by adapting some, but not all, recommendations from different guidelines.

The degree to which a recommendation is based on expert opinion of the working group and/or the Provincial Tumour Team members is explicitly stated in the guideline recommendations. Similar to the American Society of Clinical Oncology (ASCO) methodology for formulating guideline recommendations, the Guideline Utilization Resource Unit (GURU) does not use formal rating schemes for describing the strength of the recommendations, but rather describes, in conventional and explicit language, the type and quality of the research and existing guidelines that were

taken into consideration when formulating the recommendations.

Following a review of the evidence by the Alberta Provincial Cutaneous Tumour Team, no changes were made to the recommendations.

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

Internal Peer Review

Description of Method of Guideline Validation

This guideline was reviewed and endorsed by the Alberta Provincial Cutaneous Tumour Team.

When the draft guideline document has been completed, revised, and reviewed by the Knowledge Management Specialist and the working group members, it is sent to all members of the Provincial Tumour Team for review and comment. This step ensures that those intended to use the guideline have the opportunity to review the document and identify potential difficulties for implementation before the guideline is finalized. Depending on the size of the document, and the number of people it is sent to for review, a deadline of one to two weeks will usually be given to submit any feedback. Ideally, this review will occur prior to the annual Provincial Tumour Team meeting, and a discussion of the proposed edits will take place at the meeting. The working group members will then make final revisions to the document based on the received feedback, as appropriate. Once the guideline is finalized, it will be officially endorsed by the Provincial Tumour Team Lead and the Executive Director of Provincial Tumour Programs.

Evidence Supporting the Recommendations

References Supporting the Recommendations

Agarwala SS. Intermediate- and high-risk melanoma. Curr Treat Options Oncol. 2002 Jun;3(3):205-17. PubMed

Balch CM, Gershenwald JE, Soong SJ, Thompson JF, Atkins MB, Byrd DR, Buzaid AC, Cochran AJ, Coit DG, Ding S, Eggermont AM, Flaherty KT, Gimotty PA, Kirkwood JM, McMasters KM, Mihm MC Jr, Morton DL, Ross MI, Sober AJ, Sondak VK. Final version of 2009 AJCC melanoma staging and classification. J Clin Oncol. 2009 Dec 20;27(36):6199-206. PubMed

BCCA protocol summary for adjuvant therapy of high risk malignant melanoma with high dose interferon (HDIFN) alpha-2b. [internet]. 2006 Jul 1

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Eggermont AM. European approach to the treatment of malignant melanoma. Curr Opin Oncol. 2002 Mar;14(2):205-11. PubMed

Guillot B, Blazquez L, Bessis D, Dereure O, Guilhou JJ. A prospective study of cutaneous adverse events induced by low-dose alpha-interferon treatment for malignant melanoma. Dermatology (Basel). 2004;208(1):49-54. PubMed

Kirkwood JM, Bender C, Agarwala S, Tarhini A, ShipeSpotloe J, Smelko B, Donnelly S, Stover L. Mechanisms and management of toxicities associated with high-dose interferon alfa-2b therapy. J Clin Oncol. 2002 Sep 1;20(17):3703-18. PubMed

Musselman DL, Lawson DH, Gumnick JF, Manatunga AK, Penna S, Goodkin RS, Greiner K, Nemeroff CB, Miller AH. Paroxetine for the prevention of depression induced by high-dose interferon alfa. N Engl J Med. 2001 Mar 29;344(13):961-6. PubMed

Sleijfer S, Bannink M, Van Gool AR, Kruit WH, Stoter G. Side effects of interferon-alpha therapy. Pharm World Sci. 2005 Dec;27(6):423-31. PubMed

Smylie M, Claveau J, Alanen K, Taillefer R, George R, Wong R, et al. Canadian Expert Panel on Malignant Melanoma. Management of malignant melanoma: best practices. 2006.

Valentine AD, Meyers CA, Kling MA, Richelson E, Hauser P. Mood and cognitive side effects of interferon-alpha therapy. Semin Oncol. 1998 Feb;25(1 Suppl 1):39-47. PubMed

Type of Evidence Supporting the Recommendations

These recommendations were adapted from: Management of Malignant Melanoma: Best Practices, 2006 (Canadian Expert Panel on Malignant Melanoma) (see the "Adaptation" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate use of adjuvant interferon for malignant melanoma

Potential Harms

- Fever, chills and rigors often occur when interferon therapy is first initiated but diminish over time.
- The incidence of severe neuropsychiatric disorders, such as depression, can be as high as 10% so close monitoring is recommended.
- Patients with psoriasis may experience a worsening of their condition.

Refer to the "Side Effects" section in the "Major Recommendations" field for a complete listing.

Contraindications

Contraindications

- Contraindications to interferon are:
  - A history of hypersensitivity to interferon-alfa (IFNα)
  - Active cardiovascular disease (myocardial infarction within 6 months, active angina, or dysrhythmias)
  - Pre-existing liver disease
  - Central nervous system disease

    - Serious psychiatric conditions (including major depression)
    - Active autoimmune disease
    - Any debilitating medical condition is a relative contraindication because of the toxicities expected
- Suicidal ideation has been reported and is a contraindication to further IFNα-2b therapy.
- If radiation is to be part of the regimen, IFNα should not be given concurrently due to the risk of skin toxicity.

Qualifying Statements

Qualifying Statements

The recommendations contained in this guideline are a consensus of the Alberta Provincial Cutaneous Tumour Team and are a synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.

Implementation of the Guideline

Description of Implementation Strategy

- Present the guideline at the local and provincial tumour team meetings and weekly rounds.
- Post the guideline on the Alberta Health Services Web site.
- Send an electronic notification of the new guideline to all members of CancerControl Alberta.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

Alberta Provincial Cutaneous Tumour Team. Adjuvant interferon for malignant melanoma. Edmonton (Alberta): CancerControl Alberta; 2014 Feb. 13 p. (Clinical practice guideline; no. CU-002). [52 references]

Adaptation

These recommendations were adapted from: Smylie M, Claveau J, Alanen K, Taillefer R, George R, Wong R, et al. Canadian Expert Panel on Malignant Melanoma. Management of Malignant Melanoma: Best Practices. 2006.

Date Released

2014 Feb

Guideline Developer(s)

CancerControl Alberta - State/Local Government Agency [Non-U.S.]

Source(s) of Funding

CancerControl Alberta

Guideline Committee

Alberta Provincial Cutaneous Tumour Team

Composition of Group That Authored the Guideline

Members of the Alberta Provincial Cutaneous Tumour Team include medical oncologists, radiation oncologists, surgical oncologists, nurses, pathologists, and pharmacists.

Financial Disclosures/Conflicts of Interest

Participation of members of the Alberta Provincial Cutaneous Tumour Team in the development of this guideline has been voluntary and the authors have not been remunerated for their contributions. There was no direct industry involvement in the development or dissemination of this guideline. CancerControl Alberta recognizes that although industry support of research, education and other areas is necessary in order to advance patient care, such support may lead to potential conflicts of interest. Some members of the Alberta Provincial Cutaneous Tumour Team are involved in research funded by industry or have other such potential conflicts of interest. However the developers of this guideline are satisfied it was developed in an unbiased manner.

Guideline Status

This is the current release of the guideline.

Guideline Availability

Electronic copies: Available from the Alberta Health Services Web site .

Availability of Companion Documents

The following is available:

- Guideline utilization resource unit handbook. Edmonton (Alberta): CancerControl Alberta; 2013 Jan. 5 p. Electronic copies: Available from the Alberta Health Services Web site .

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on August 12, 2014. The information was verified by the guideline developer on September 22, 2014. This summary was updated by ECRI Institute on September 21, 2015 following the U.S. Food and Drug Administration advisory on non-aspirin nonsteroidal anti-inflammatory drugs (NSAIDs). This summary was updated by ECRI Institute on June 2, 2016 following the U.S. Food and Drug Administration advisory on Opioid pain medicines.

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